

Remarks

Claims 38-87 were pending in the subject application. By this Amendment, claims 38-40, 43-45, 46, 48-52, 55-57, 59-62, 65-69, 72-74, 76, 77, 79, 80, and 82-87 have been amended, and new claims 88 and 89 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 38-89 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The applicant would like to bring to the Examiner's attention a supplemental Information Disclosure Statement (IDS) listing references for consideration in the prosecution of the subject application which is being submitted in conjunction with the filing of this Amendment. The applicant respectfully requests that the references be considered and made of record by the Examiner in the subject application.

By this Amendment, claims 38-40, 45, 46, 48-52, 57, 59-62, 74, 76, 77, 79, 80, and 82 have been amended to more clearly indicate that the interfering RNA or hybridizing nucleic acid molecule is administered to a human or mouse. The term "mammal" has been removed from the claims. Claims 67-69 and 83-87 have been amended to remove the term "pharmaceutical". New claims 88 and 89 recite that the interfering RNA and hybridizing nucleic acid molecule, respectively, are administered *ex vivo*. Support for claims 88 and 89 can be found at page 13, lines 18-25, of the specification.

The Examiner indicates that the sequences in the Sequence List submitted with the applicant's previous Response were not provided in the specification as originally filed. A Submission of Sequence Listing, including a sequence listing on paper and computer readable format, was submitted with the applicant's previous Response in reply to a Notice to Comply with Requirements for Patent Applications Containing Nucleotide and/or Amino Acid Sequence Disclosures. A copy of the Notice was submitted with that Response. The applicant respectfully submits that all the sequences in the Sequence Listing (SEQ ID NOs:1-4) are merely the primers found at page 20, lines 1-8, of the patent application as originally filed. SEQ ID NOs:1-4 are not the

RNAi sequences described in Dr. Kerr's Declaration under 37 C.F.R. §1.132. Thus, these sequences do not constitute new matter. The subject application is in compliance with 37 C.F.R. §1.821-1.825.

Claims 38-87 have been rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. The applicant traverses and respectfully submits that the subject specification provides a sufficient written description of the claimed invention.

The Office Action indicates that the subject application does not adequately describe the concise structural features that distinguish molecules within the recited genera of interfering RNA specific for human or mouse SHIP-1 mRNA (claims 57-73) and nucleic acid molecules that hybridize with human or mouse SHIP-1 mRNA (claims 74-87) from those outside the genera. Further, the Office Action indicates that the subject application does not provide a representative number of species for either of the genera claimed.

The subject specification contains sufficient disclosure to convey to one of ordinary skill in the art that the applicant had possession of the concept of what is claimed, which is all that is necessary to satisfy the written description requirement under 35 U.S.C. §112, first paragraph. The teaching of the subject application and knowledge of the sequence and structure of the SHIP-1 gene provides sufficient structural and functional correlates to describe the genera of interfering RNA and hybridizing nucleic acid molecule recited in the claims. As indicated in Dr. William Kerr's Declaration under 37 C.F.R. §1.132 dated July 16, 2004 (referred to herein as the Kerr I Declaration), the mRNA sequences of mouse and human SHIP-1 have been publicly available since the late 1990s, as evidenced by Exhibits B and C (National Center for Biotechnology Information (NCBI) accession numbers NM_10566 and NM_005541, respectively), which accompanied the Declaration. The applicant submitted Exhibit A with Dr. Kerr's Declaration under 37 C.F.R. §1.132 dated January 18, 2005 (hereinafter referred to as the Kerr II Declaration), which contained mammalian orthology data for SHIP-1 obtained from the NCBI Homologene data base. Exhibit A includes a table of pair wise alignment scores showing that the degree of nucleotide homology between mouse and human SHIP-1 is over 88%.

RNA mediated interference or RNA interference (RNAi) is a term initially coined by Fire and co-workers to describe the phenomenon that double-stranded RNA (dsRNA) can block gene expression when it is introduced into nematodes (Montgomery, M.K. *et al. Proc. Natl. Acad. Sci.*

USA, 1998, 95:15502-15507, which accompanies the supplemental IDS submitted herewith). RNAi has become a potent tool for suppressing gene expression in mammalian cells at the mRNA level utilizing a process of sequence-specific, post-transcriptional gene silencing. Accompanying the supplemental IDS submitted herewith are International Publication WO 99/32619 (Fire *et al.*), Tuschl T. *et al.* (*Genes & Development*, 1999, 13:3191-3197); Zamore P. *et al.* (*Cell*, 2000, 101:25-33); Svoboda P. *et al.* (*Development*, 2000, 127:4147-4156); Tuschl, T. *et al.* (*Chembiochem*, 2001, 2(4):239-245); Elbashir S. *et al.* I (*Nature*, 2001, 411:494-498); Elbashir S. *et al.* II (*Genes & Development*, 2001, 15:188-200) and Caplen N.J. *et al.* (*PNAS*, 2001, 98(17):9742-9747). RNAi is triggered by dsRNA and results in sequence-specific degradation of homologous single-stranded target RNAs. When dsRNA containing a sequence complementary to a specific mRNA target is administered to cells, it is processed into short nucleotide fragments that guide the cleavage of the transcript. Thus, the endogenous mediators of RNAi are short (*e.g.*, 21-23-nucleotide) interfering RNAs (siRNAs) generated from the longer double-stranded RNAs by the ribonuclease III activity of the highly conserved dicer enzyme (Tuschl T. *et al.* (1999); Zamore P. *et al.*; Elbashir S. *et al.* I; and Elbashir S. *et al.* II). It has been demonstrated that RNAi-mediated gene suppression can be obtained in mammalian cells by delivery of chemically synthesized short (*e.g.*, less than 30 nucleotides) double-stranded siRNA molecules or by endogenous expression of short hairpin RNAs (shRNAs) bearing a fold-back stem-loop structure (Elbashir *et al.* I).

The interfering RNA and hybridizing nucleic acid molecules recited in the claims are not described by function alone. As is evidenced by the aforementioned publications, structural attributes of interfering RNA, including size and content, were known in the art at the time the application was filed (see, for example, pages 197-198 of Elbashir S. *et al.* II). Elbashir *et al.* proposed directly introducing short (*e.g.*, 21-23 nucleotides) dsRNA (siRNA) into mouse and human cells to avoid the problems associated with the expression of longer dsRNAs (Elbashir S. *et al.* I). Elbashir *et al.* state,

The finding that synthetic 21- and 22-nt siRNA duplexes can be used for efficient mRNA degradation demonstrates that the targeting step can be uncoupled from the dsRNA-processing step. This raises the prospects of using siRNA duplexes as new tools for sequence-specific regulation of gene expression in functional genomics as well as biomedical studies. The siRNA may be effective in mammalian

systems, where long dsRNAs cannot be used because they activate the dsRNA-dependent protein kinase (PKR) response (Clemens 1997). As such, the siRNA duplexes may represent a new alternative to antisense or ribozyme therapeutics. (Elbashir S. *et al.* II, page 198, column 2)

The state of the art of RNAi at the application's filing date, combined with the teachings of the subject application, provide a rational basis for the design of interfering RNA specific for SHIP mRNA. To target a specific mRNA for degradation, a portion of the mRNA sequence must be known and a segment of the target mRNA must be selected that will be used for targeting by the cognate siRNA duplex. The design of specific siRNA duplexes that interfere with the expression of a specific gene requires accurate knowledge of at least a 20-nucleotide segment of its encoded mRNA. These requirements are met by the subject application. Having the structure and sequence of the target gene (SHIP-1), and the teachings of the specification, the applicant submits that one skilled in the art would readily envision target nucleic acid sequences with the SHIP mRNA sequence, such as the SHIP-1 enzymatic domain. Furthermore, due to the certainty of the genetic code and complementarity, there is a well known correlation between target nucleic acid sequences within a target gene and nucleic acid sequences that interfere with the expression of the target gene. Hence, having the nucleotide sequence of the target gene provides sufficient information to one skilled in the art to obtain the interfering RNA molecules and hybridizing nucleic acid molecules recited in the claims. Therefore, the applicant respectfully submits that the subject specification provides sufficient information regarding the genus of SHIP-1 mRNA as well as hybridizing nucleic acid molecules and interfering RNA specific thereto. As the Examiner is aware, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984).

With regard to interfering RNA, while it is true that not all RNA molecules will inhibit a target gene, the availability of the entire human and mouse SHIP-1 gene sequence, the capability to synthesize potentially interfering RNA molecules in large quantities, and the knowledge available to

those skilled in the art at the time the application was filed (*e.g.*, International Publication WO 99/32619 (Fire *et al.*); Tuschl T. *et al.* (1999); Zamore P. *et al.* (2000); Svoboda P. *et al.*, (2000); Tuschl, T. *et al.* (2001); Elbashir S. *et al.* I (2001); and Elbashir S. *et al.* II (2001)) increase the likelihood of obtaining functioning interfering RNA molecules specific for SHIP-1. Thus, while the predictability that any single interfering RNA molecule will be effective in gene silencing is not necessarily high, the probability of identifying an individual functional interfering RNA molecule among rationally designed candidates is very high, and hence predictable.

The descriptive text needed to meet the written description requirement varies with the nature and scope of the invention at issue, and with the scientific and technological knowledge already in existence. There is no *per se* rule that in order to satisfy the written description requirement, known DNA sequences must be disclosed in the specification. Rather, the written description requirement must be considered in the context of the claimed invention and the state of knowledge in the relevant art. *Capon et al. v. Eshhar et al.*, 418 F.3d, 1349 (Fed. Cir. 2005). In *Capon et al.*, which is a case stemming from a patent interference between two parties each claiming chimeric cell surface receptors, the U.S. Court of Appeals for the Federal Circuit struck down as “an inappropriate generalization” the Board of Patent Appeals and Interference’s rule that, even where the nucleotide sequences of the component DNA are known, the nucleotide sequences of the chimeric genes must be fully presented. The Court noted “the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter.” As explained by the Court:

[I]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention.

Thus, the written description requirement states that the applicant must describe the invention; it does not state that every invention must be described in the same way. The applicant acknowledges that sequences and structural formulas provide a convenient method of demonstrating possession of many molecules; however, other identifying characteristics or combinations of

characteristics may demonstrate the requisite possession. In *Enzo Biochem, Inc. v. Gene-Probe, Inc.*, 63 USPQ2d 1609 (Fed Cir. 2002), the Court reaffirmed that deposit of a physical sample may replace words when description is beyond present scientific capability. In *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 65 USPQ2d 1385 (Fed Cir. 2003), the Court explained further that the written description requirement may be satisfied “if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.” For example, possession of an antibody may be demonstrated based on a description and characterization of its corresponding antigen. Disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen. *Noelle v. Lederman*, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) and MPEP 2163 IIA3(a). The nature of the interfering RNA and hybridizing nucleic acid molecules of the invention are clearly distinguishable from the compounds at issue in *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004), where the Court affirmed that the description of the COX-2 enzyme did not serve to describe unknown small molecules capable of selectively inhibiting the enzyme. The teaching of the subject specification and the knowledge of the sequence and structure of the SHIP gene provides one skilled in the art with sufficient structural and functional correlates to describe the genus of interfering RNA and hybridizing nucleic acid molecules that suppress expression of the SHIP gene.

Having the nucleotide sequence of the target gene provides discerning information regarding the sequences of suitable interfering RNA molecules, and leads one of ordinary skill in the art to their selection. Due to nucleotide complementarity and the mechanism of RNAi, RNA molecules likely to hybridize with SHIP mRNA and interfere with its expression could then be determined. One of ordinary skill in the art need only be provided with the sequence of the target gene, as opposed to the sequence of any particular interfering RNA. There is no sequence information essential for carrying out the invention that is not provided in the specification or not well known to those skilled in the art.

Thus, the applicant submits that the subject specification contains sufficient disclosure to convey to one of ordinary skill in the art that the applicant had possession of the concept of what is claimed, which is all that is necessary to satisfy the written description requirement of 35 U.S.C.

§112, first paragraph. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 38-87 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicant respectfully traverses and submits that the claimed invention is fully enabled by the subject specification.

The compositions and methods of the claimed invention are reasonably enabled by the specification, as one of ordinary skill in the art would be able to make and use the invention without undue experimentation. As an initial matter, the applicant wishes to point out to the Examiner that claims 67-73 and 83-87 are drawn to compositions comprising, respectively, interfering RNA specific for human or mouse SHIP-1 mRNA and a nucleic acid molecule that hybridizes with human or mouse SHIP-1. As the Examiner is aware, “when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use” (emphasis added) MPEP 2164.01(c). As taught at page 11, lines 31-34, and page 13, lines 18-25, inhibitors of SHIP can be administered to cells *ex vivo*. Furthermore, one skilled in the art would appreciate the value of the claimed compositions for the analysis of SHIP gene function *in vitro*. Thus, the issues raised in the Office Action pertaining to *in vivo* delivery of the interfering RNA or hybridizing nucleic acid molecule are inapplicable to the composition claims of the subject application. Furthermore, by this Amendment, the applicant has added claims 88 and 89, which recite that the interfering RNA and nucleic acid molecule, respectively, are administered. Thus, the issues raised in the Office Action pertaining to *in vivo* delivery of the interfering RNA or hybridizing nucleic acid molecule are inapplicable to claims 88 and 89, as well.

By this Amendment, claims 38-40, 45, 46, 48-52, 57, 59-62, 74, 76, 77, 79, 80, and 82 have been amended to more clearly indicate that the interfering RNA or hybridizing nucleic acid molecule is administered to a human or mouse. The term “mammal” has been removed from the claims. The issues raised in the Office Action concerning the predictability of suppressing SHIP expression and treatment effects in any (and all) mammals are inapplicable to the currently pending claims.

At pages 7-15, the Office Action cites various issues concerning stability and delivery of nucleic acid based therapeutics. To the extent the applicant’s remarks set forth above in response to

the rejection under 35 U.S.C. §112, first paragraph, for lack of written description, are applicable to the non-enablement rejection, the remarks are incorporated herein by reference. As the applicant stated above, having the structure and sequence of the target gene (SHIP), the applicant submits that one skilled in the art could readily obtain target sequences within the recipient's SHIP mRNA. Furthermore, due to the certainty of the genetic code and complementarity, there is a well known correlation between target nucleic acid sequences within a target gene and nucleic acid sequences that interfere with the expression of the target gene. Hence, having the nucleotide sequence of the target gene provides sufficient information to allow one skilled in the art to obtain candidate interfering RNA molecules without resort to undue experimentation.

While it is true that not all RNA molecules will inhibit a target gene, the availability of target gene sequence information, the capability to synthesize potentially interfering RNA molecules in large quantities, and the knowledge of those skilled in the art increase the likelihood of obtaining gene silencing RNA molecules. Thus, the probability of finding an individual functional interfering RNA molecule among rationally designed candidates is very high, and screening for such RNA molecules does not involve undue experimentation. The results achieved with the SHIP-specific interfering RNA in the experiments described in the Kerr I and Kerr II Declarations is reasonably predictive of other interfering RNA specific for SHIP.

As the Examiner is aware, a specification is initially presumed to be in compliance with the enablement requirement of §112, first paragraph. The burden is on the Patent Office to establish a reasonable basis to question enablement. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The test of enablement is whether one of ordinary skill in the art could make and use the claimed invention from the teachings of the patent application, coupled with information known in the art, without undue experimentation. For an Office Action to sustain a rejection on the grounds of enablement, it must provide evidence that the claimed method could not be performed without undue experimentation.

In the section of the Office Action pertaining to the state of the prior art and the predictability or unpredictability of the art at pages 7-8, the Office Action cites publications concerning antisense oligonucleotides and ribozymes. None of these references appear to consider interfering RNA. The applicant submits that while the currently pending claims of the subject application are fully enabled,

it is art-recognized that RNAi differs from antisense-mediated interference in both approach and effectiveness. Antisense-mediated genetic interference requires delivery to a cell interior of specific-single-stranded nucleic acid molecules at a concentration that is equal to or greater than the concentration of endogenous mRNA. RNAi has advantages over antisense both in the stability of the material to be delivered and the concentration required for effective inhibition (see page 2, lines 12-29, and page 4, lines 14-25, of International Publication WO 99/32619 (Fire *et al.*). Furthermore, compared to antisense or ribozyme technology, the secondary structure of the target mRNA does not appear to have a strong effect on RNAi-mediated silencing (see Harborth J. *et al.*, *J. Cell Sci.*, 2001, Dec., 114 (Pt. 24):4557-4565, which accompanies the supplemental IDS submitted herewith). In fact, RNAi has now become such a popular tool for gene silencing, many companies use proprietary algorithms to design and chemically synthesize siRNAs using a conventional DNA/RNA synthesizer. Research groups have created human shRNA libraries that target thousands of genes and used them to identify new genes (see pages 80-81 and 84 of Bonetta, L. "RNAi: Silencing never sounded better" *Nature Methods*, 2004, 1(1):79-86), which accompanies the supplemental IDS submitted herewith).

At page 9, the Office Action states that the experimental data submitted with the Kerr I and Kerr II Declarations is not representative of treatment effects such as altering NK function, preventing transplant rejection in any patient, or preventing or treating graft versus host disease (GVHD) in any mammal following administration of RNAi. The proper standard for compliance with the enablement requirement is not absolute predictability but objective enablement. Evidence provided by the applicant needs not be conclusive but merely convincing to one of skill in the art (see MPEP 2164.05). In other words, a patent specification need not set forth clear and convincing evidence "proving" its conclusions. Rather, the applicant's statements and assertions are to be taken as true, and rejected only if the underlying facts are found to be untruthful or inaccurate, *i.e.*, only if the asserted claim is "incredible" or "impossible." *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971).

The experimental evidence in the subject specification is sufficiently compelling and fully supports the assertion that SHIP-1 plays a dominant role in graft rejection and that suppressing the function of SHIP-1 in the clinically relevant cells (hematopoietic cells) alters NK cell functions and

reduces or eliminates the severity of transplant rejection in humans or mice. The experimental data submitted with the Kerr I and Kerr II Declarations show that SHIP-1-specific interfering RNA can be successfully delivered using methods for delivering nucleic acid molecules taught in the subject application and available to those skilled in the art at the time the application was filed. Furthermore, the interfering RNA were delivered in sufficient amounts to have profound physiological effects in a rapid fashion, even when complete knockdown was not achieved (see page 15 of the applicant's Amendment submitted February 7, 2005). In the Kerr II Declaration, Dr. Kerr indicates that "... even partial induction of SHIP-1 deficiency *in vivo* can increase the representation of cells capable of suppressing allogeneic T cell priming. A reduced allogeneic T cell response is considered by those in the field as a key determinant to successful engraftment" (Kerr II Declaration, page 5, section 8). Figures A-C of Exhibit C, which accompanied the Kerr II Declaration, show that induction of SHIP-1 deletion in the adult MXCreSHIPflox/- mice increases MSC numbers in the lymph node (LN) and spleens of mice, and leads to compromised priming of allogeneic T cells. This does not require complete ablation of SHIP-1 expression, as mice with partial SHIP-1 ablation also show significantly reducing priming of allogeneic T cells. As indicated by Dr. Kerr in the Kerr II Declaration, "the MXCre mouse represents a stringent model for assessment of altered SHIP-1 function, and is recognized by those in the field as a valid tool for determining the physiological effects of endogenous gene ablation *in vivo*" (Kerr II Declaration, page 5, section 8). Furthermore, Figures D and E of Exhibit C, which accompanied the Kerr II Declaration, show that SHIPflox/- mice with myeloid-specific expression of Cre (LysCre) can have a significant increase in MSC that leads to profound suppression of allogeneic T cell priming. "Again, only a partial deletion of SHIP-1 in the myeloid lineage is required to achieve significant suppression of allogeneic T cell responses, which mediate GVHD and organ graft rejection ... [t]hus, this physiologic response is clinically favorable and reasonably correlates with a therapeutic benefit in mediating GVHD and organ graft rejection" (Kerr II Declaration, page 5, section 8). In view of the evidence submitted to the Patent Office, it is certainly not "unreasonable" for the applicant to suggest that graft rejection can be treated or prevented by inhibiting SHIP function and the physiological activity associated therewith.

In regard to animal models, the applicant submits that all that is required by the patent laws is that a "reasonable correlation" exist between the scope of the claims and the scope of enablement. *In*

re Brana, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) and MPEP 2164.02. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 224 USPQ 739, 747 (Fed. Cir. 1985):

[B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

If a particular model is recognized as correlating to a specific condition, then it should be accepted as such unless there is evidence that the model does not correlate. Since the initial burden is on the Examiner to give reasons for lack of enablement, reasons must also be given for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. Thus, the applicant respectfully submits that the models within the specification and exhibits accompanying the Kerr I and Kerr II Declarations are sufficiently predictive of graft rejection. As such, the pending claims are commensurate in scope with the experimental findings of the instant disclosure and enabled thereby.

The applicant respectfully submits that an application for patent is not required to show that a claimed method of treatment of a disease condition results in a cure of that disease condition, or even that clinical efficacy is achieved. The Federal Circuit has made it clear that the showing for therapeutic utility that is sufficient to satisfy the patent laws is not to be confused or equated with the showing required by the Food & Drug Administration for drugs, medical devices, and procedures. *Scott v. Finney*, 32 USPQ2d 1115 (Fed. Cir. 1994) and Manual of Patent Examining Procedure 2164.05. Given the state of the art as demonstrated by the scientific publications submitted herewith, and the information provided in the subject specification and the experimental results obtained therewith, one of ordinary skill in the art can target and reduce expression of SHIP *in vitro* or *in vivo*, without resort to undue experimentation. Thus, the applicant respectfully submits that the subject specification enables the compositions and methods as currently claimed.

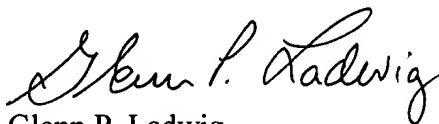
The applicant respectfully submits that the subject specification contains sufficient information to enable one of ordinary skill in the pertinent art to make and use the claimed invention without undue experimentation. Accordingly, the applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

In view of the foregoing remarks and amendments to the claims, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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